

DETAILED ACTION

The amendment filed 06/09/2010 has been entered. Claims 7 and 9 are pending and being examined.

Maintained formal matters, objections, and/or rejections:

- 5 The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

- 10 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- 15 Claims 7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the migration of HMVECs in vitro using Slit2 ligand, does not reasonably provide enablement for a method of inhibiting the migration of HMVECs without regard to the system in which the Slit ligand is employed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate
20 in scope with these claims.

Response to Arguments

Applicant argues that:

- 25 ...the teachings and experimental support provided by the specification specifically support the invention as it is recited in the pending claims, allowing one of ordinary skill in the art to not only appreciate the invention, but to make and use the invention as it is claimed.

...The teachings and guidance included in the specification of the present application, including the experimental evidence provided therein, specifically support such methods. ...When the experimental results detailed in the specification are combined with the specific teachings provided by the specification, such as those found in paragraphs [0042]-[0045] and [0050]-[0052], one of ordinary skill in the art would be equipped with information sufficient to practice the full scope of the methods, including *in vitro* and *in vivo* methods, recited in the pending claims.

...the enablement requirement does not dictate that the specification provide working examples describing every embodiment of a claimed invention, only that the specification as a whole allow one of ordinary skill to practice the invention without undue experimentation. (See, M.P.E.P. § 2164.02).

Applicants' arguments have been fully considered but they are not persuasive.

The examiner did not make a requirement that the specification provide working examples of every embodiment of the claimed invention. However, the examiner did indicate that the claims encompass *in vitro* and *in vivo* methods of inhibiting the migration of HMVECs whenever and wherever HMVEC migration is occurring. The full scope of a claim must be enabled. The one working example in the specification is limited to disclosing that Slit2 inhibits the migration of HMVECs expressing Robo4 (paragraph [0045]) in an *in vitro* cell migration assay (Figure 7). The examiner did find that Applicants' enablement of one mode of practicing the invention (an *in vitro* method of inhibiting the migration of HMVECs expressing a native Robo4 receptor with slit2) was not sufficient to enable the full scope of the claimed invention because the rejection of record cited references that found results counter those disclosed and claimed in the present application, and held that there is a lack of predictability in the art, angiogenesis and vascular guidance are complex, and the working examples and guidance in the specification are limited.

The examiner uses Wang (Cancer Cell. 2003 Jul;4(1):19-29) to establish that, after the filing date, it was not possible to carry out the full scope of the claimed invention because Wang's results indicate that Slit2 can promote angiogenesis and microvessel migration *in vivo*. Although Wang is concerned with Robo1 signaling, the results of Okada (Circ Res. 2007 Jun 22;100(12):1712-22) indicate that microvascular endothelial cells express a native Robo-4 receptor, and that Wang's results, that are opposite to those claimed, are not due to a lack of Robo-4 expression in Wang's experimental system. The examiner believes Okada is relevant in this regard.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geng (U. S. Publication No. 20030236210) in view of Goldberg (U. S. Patent No. 5,480,975).

Response to Arguments

Applicant argues that:

...In direct conflict with the current claims, Geng teaches that Slit2 induces the migration of HMVECs. ...Geng teaches directly away from the claimed invention by teaching that Slit2 induces HMVEC migration.

...an unknown inherency cannot be the basis of an obviousness rejection and, at the time of the application, it was not known that Slit2 inhibits HMVEC migration. ...obviousness cannot be predicated on what is not

known at the time an invention is made, even if the inherency of a certain feature is later establishedbecause the alleged inherency of Slit2 inhibition of HMVECs was not known at the time of the application, and was only established by the current inventors, the current claims could not be found obvious under § 103, and the Examiner's assertions must fail.

...the concept of inherent anticipation under § 102 simply cannot be applied in the same way to obviousness determinations under § 103. ... the analysis for obviousness cannot be based on what is unknown. The suggestion or motivation to combine or modify references required to establish a prima facie case of obviousness, must occur prior to the application date, and an unknown inherency cannot supply this suggestion or motivation at the required time without resorting to impermissible hindsight. ...an unknown inherency cannot be a basis for obviousness because one of ordinary skill in the art could not have had access to the unknown subject matter, and, therefore, could not have relied on the unknown subject matter in the prior art to practice the claimed invention. Therefore, without the benefit of impermissible hindsight, an unknown inherency in a prior art reference cannot be the basis of a prima facie case of obviousness.

...the possibility of Slit2 inhibiting HMVEC was not even present in the prior art because Geng teaches directly away from the use of Slit2 for inhibiting HMVEC migration. ...Geng does not make it clear that HMVEC migration may be inhibited with Slit2, and therefore, it does not establish inherency of the same. As such, the subject matter of the current claims was not, in fact, inherent in the cited reference. (See, e.g., MPEP 2112(11) "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp., 339 F.3d at 1377, 67 USPQ2d at 1668).

It was only after the work performed by the current inventors, that the inhibition of HMVEC migration by Slit2 was discovered. ...only with impermissible hindsight, the benefit of applicants' disclosure, and reliance on an unknown inherency, would it be possible for cited art to arrive at the subject matter claimed in the present claims.

... there would have been no motivation, predictable results, or reasonable expectation of success for one of skill in the art to try and use the teachings of Geng to inhibit HMVEC migration using Slit2. The only prediction or reasonable expectation in view of Geng would be that Slit2 would promote HMVEC migration, exactly the opposite result required by the subject matter recited in current claims (see, e.g., paragraph [0014]

and FIG. 2 of Geng). The fact that applicants' discovery runs contrary to the understandings forwarded by Geng and establishes that Slit2 inhibits migration of HMVECs is the touchstone of patentability and only highlights the significance of the claimed invention.

5 ...Geng does not teach and could never be understood to teach the inhibition of HMVEC migration through the use of Slit2 as required by the pending claims. Accordingly, one of skill in the art, after reading Geng, would expect that exposing HMVECs to Slit2 could only induce the migration of the HMVECs. This teaching of Geng is directly contradictory to the current claims 7 and 9 that are directed to a method of inhibiting the migration of HMVECs. In fact, Geng teaches directly away from the claimed invention by teaching that Slit2 induces HMVEC migration. Therefore, contrary to what has been asserted by the Examiner, the current claims do not "naturally flow from following the teaching of Geng in view of Goldberg."

Applicants' arguments have been fully considered but they are not persuasive.

The obviousness rejection is not predicated on what is not known at the time of

20 invention, i.e., inhibition of HMVEC migration by Slit-2. Rather, the obviousness rejection is predicated on the suggestion or motivation to administer Slit-2 to humans to treat hypoxia. Inherency is not relied upon to provide motivation or suggestion to combine the references. The claims only require exposing HMVECs expressing a native Robo-4 receptor to a Slit-2 ligand. Inhibiting the migration of HMVECs is an intended use or outcome of the claimed method. The method suggested by Geng in view of Goldberg cannot be practiced without exposing HMVECs expressing a native Robo-4 receptor to a Slit-2 ligand. Inhibiting the migration of HMVECs expressing a native Robo-4 receptor would naturally flow from following the teachings of Geng in view of Goldberg. Applicants' arguments do not address the motivation or reasonable expectation of success for one of ordinary skill in the art to administer Slit-2 to humans to treat hypoxia.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY NICKOL, CAN BE REACHED AT (571) 272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-0835.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE [HTTP://PAIR-DIRECT.USPTO.GOV](http://PAIR-DIRECT.USPTO.GOV). CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647